Kyper & Associates

Consultants to the Medical Device Industry

March 17, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 98D-1134
Proposed Rule re Reclassification of Electrocorporeal Shock Wave Lithotripters

Dear Sir/Madam:

On behalf of a holder of an approved premarket approval application (PMA) for an electrocorporeal shock wave lithotripter (ESWL), we are submitting the enclosed comments on the above referenced proposed rule. My client is supportive of this FDA proposed rule to reclassify this device from Class III (premarket approval) into Class II (special controls) under 21 CFR 876.5990 (Electrocorporeal shock wave lithotripter). Under separate cover to Docket No. 98D-1165 we have submitted comments on the "Draft Guidance for the Content of Premarket Notifications [510(k)s] for Electrocorporeal Shock Wave Lithotripters Indicated for the Fragmentation of Kidney and Ureteral Calculi." Because FDA has designated this guidance, when finalized, as a special control for reclassified ESWLs, we have included our comments on the draft guidance as an enclosure with this letter. FDA should also address these comments in the preamble to the final order reclassifying ESWLs.

FDA Use of Premarket Approval Application Data

Section 216 of the FDA Modernization Act of 1997 (FDAMA) amended section 520(h)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) to make available safety and effectiveness information in an approved PMA for FDA use, among other things, in approving or reclassifying another device 6 years after FDA approval of the PMA. As indicated in FDAMA and the proposed reclassification rule, the publicly available summaries of safety and effectiveness information required by section 520(h)(1)(A) of the Act are thereby available to FDA as the evidentiary basis for FDA approval or reclassification of another device.

Reclassifications must be supported by sufficient valid scientific evidence, as defined under 21 CFR 860.7, that provides reasonable assurance that the generic type of device is safe and effective for its intended use. The safety and effectiveness information in the approved PMAs for ESWLs would be expected to provide the highest level of valid scientific evidence possible. Safety and effectiveness information reported in the medical literature rarely meets the criteria for valid scientific evidence under 21 CFR 860.7 and is usually insufficient to

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provide reasonable assurance of safety and effectiveness. The proposed rule does not identify, and the cited references placed upon display in the Dockets Management Branch do not include, the summaries of the safety and effectiveness for the approved PMAs for ESWLs made available for FDA use under section 216 of FDAMA and used by the FDA and the Gastroenterology and Urology Devices Advisory Panel as the primary basis for the proposed reclassification. These summaries should be immediately added to the supporting documents on display in the Dockets Management Branch and then identified in a *Federal Register* notice.

Neither section 216 of FDAMA nor the proposed rule addresses the availability for FDA use of safety and effectiveness information in approved PMA supplements for ESWLs. PMA supplements were established in the PMA procedural regulation (21 CFR Part 814) as an alternative to a new PMA when a device is modified in a manner that affects its safety or effectiveness. As such, the 6-year provision in section 216 should also apply to approved PMA supplements in terms of the availability of the safety and effectiveness information therein for FDA use in approving or reclassifying another ESWL device.

Predicate devices cited in premarket notification [510(k)] submissions, by other than the holder of the approved PMA/PMA supplement for the cited predicate device, should be limited to model numbers or modified versions of ESWLs legally marketed under (1) a FDA cleared 510(k) submission or (2) a PMA or PMA supplement approved no sooner than 6 years before the applicant's 510(k) submission for a new or modified ESWL. Holders of approved PMAs at the time of the final reclassification regulation should be the only 510(k) applicants permitted to cite as the predicate device a model number or modified version of their ESWL cleared for marketing under their approved PMA or PMA supplement within the preceding 6 years. In both cases the differences between the technological characteristics of their new or modified device and the cited predicate device would then be subject to the provisions of section 513(i)(1)(A)(ii) of the Act for the purpose of demonstrating substantial equivalence. This position should be reflected in the final 510(k) guidance and the preamble for the final reclassification regulation. If FDA disagrees with this position, both documents should include appropriate justifications for the FDA position in this matter.

It may be questionable whether a 510(k) applicant, other than the holder of the approved PMA supplement for the cited predicate device, can claim that its ESWL is substantially equivalent to a device previously marketed under an approved PMA supplement. Summaries of the safety and effectiveness information supporting PMA supplement approvals are not required by section 520(h)(1)(A) of the Act and have only been prepared for a significant new intended use for an existing PMA approved device. No such summaries for PMA supplement approvals are presently available for FDA use as the evidentiary basis for clearing or approving another firm's ESWL under section 216 of FDAMA. A holder of an approved PMA supplement, however, retains the right to reference information therein in support of a 510(k) submission for a significant modification of its device. Prior to reclassification the PMA holder can readily protect the continued confidentiality of this information by requesting that FDA, at the time of the reclassification, convert its approved PMA supplements to a Device Master File for the firm's exclusive use. The FDA position in this matter should be enunciated in the ESWL 510(k) guidance and the preamble for the final reclassification regulation. The final

510(k) guidance should be released in advance of the final reclassification regulation so that PMA holders can take, if possible, appropriate measures to protect the continuing confidentiality of their PMA supplement safety and effectiveness information.

Intended Use

The suggested indication for use in the draft ESWL 510(k) guidance and the proposed ESWL classification regulation (21 CFR 876.5990) are inconsistent with that in PMA/PMA supplement approvals for ESWLs to date. In the latter case the approved indication for use usually includes limitations on the size range of the urinary stones to be fragmented and the region of the ureter to be treated. No such limitations appear in the intended use statement under proposed 21 CFR 876.5990 (i.e., "fragment urinary calculi within the kidney and ureter") or in the draft guidance [i.e., "fragment urinary stones in the kidney (renal pelvis and renal calyces) and ureter (upper, middle, and lower ureter)"].

The Appendix to proposed 21 CFR 876.5990 establishes labeling restrictions as a special control for reclassified ESWLs. These labeling restrictions do not address the indication for use. They include precautions regarding the limited effectiveness of treating staghorn or large (20 mm and greater in largest dimension) stones, the risk of treating small (4 to 6 mm in largest dimension) stones in the middle and lower ureter, and the risk of treating lower ureteral stones in women of childbearing age. Does FDA now believe that a precaution rather than the indication for use or a warning is the appropriate approach to placing a limitation on use? If so, the final rule and final 510(k) guidance should indicate what holders of approved PMAs should do to remove, if they so desire, any existing limitations in the FDA required indication for use statement for their ESWL in order to be consistent with the indication for use in the final rule and final 510(k) guidance. FDA should ensure consistency in the labeled intended use for ESWLs.

Clinical Performance Testing

The suggested confirmatory clinical study in the draft 510(k) guidance for demonstrating substantial equivalence would permit as few as 20 patients to be enrolled at two investigational sites with only a follow-up at 1-week post-procedure. The draft guidance is unclear whether there should be at least 20 patients enrolled at each of two sites or a total of 20 patients between two sites. Either way, a clinical study of such low magnitude does not lend itself to any meaningful statistical evaluation. On a random selection basis, it would not be expected to enroll patients representative of the patient population in the indication for use statement suggested in this draft guidance and discussed in the preceding section. If the final guidance continues to provide for confirmatory clinical studies of this low magnitude, it should justify the adequacy of such studies in demonstrating substantial equivalence.

For a new or significantly modified ESWL with an operating principle and shock wave characteristics similar to the cited predicate device(s), a confirmatory clinical study for demonstrating substantial equivalence should involve at least 3 investigational sites, a minimum of 30 patients per site, and the assessment of treatment success and adverse effects immediately post-procedure and at 2-weeks and 1-month thereafter. This study lends itself to

a meaningful statistical evaluation and should allow for a study population representative of the intended use. It should also permit the 510(k) applicant and FDA to determine whether the success rate is consistent with marketed ESWLs and whether its adverse event experience is consistent with the standardized adverse event information to be required in the labeling.

We support the provision on page 9 of the draft guidance that the addition of device-specific claims regarding the clinical performance of the applicant's ESWL must be demonstrated by sufficient clinical data to statistically support the claim. The draft guidance should be revised to clearly indicate that such a claim requires FDA clearance of a 510(k) before it can be included in the firm's labeling, advertisements, and other promotional materials for its device. We are concerned, however, that FDA apparently lacks the authority to revoke 510(k) clearances and may grant 510(k) clearances for comparative performance claims based upon flawed or inadequate studies. The confirmatory clinical studies suggested in the draft guidance will obviously not provide study populations comparable to those in approved PMAs and cannot statistically support claims of superior safety and effectiveness. We suggest that the guidance clearly indicate that FDA will not accept 510(k) submissions for comparative performance claims as such claims are inappropriate for 510(k) review and, in all likelihood, are unsupportable for substantially equivalent devices. The guidance should identify the types of clinical performance claims that FDA deems appropriate for 510(k) review and clearance.

Labeling Restrictions

Because ESWLs are presently, and will continue to be, restricted devices and not simply prescription devices under 21 CFR 801.109, the restricted device legend should be revised to read:

> "CAUTION: Federal law restricts this device to sale, distribution, and use only upon the lawful order of a physician trained and/or experienced in the use of this device as outlined in the required training program."

The legend in the proposed rule and draft guidance is consistent with 21 CFR 801.109 for prescription devices and, as such, only restricts the sale, and not the distribution and use, of the device. The suggested revision reflects the FDA intent in this matter (i.e., restricted use) and conforms to the restricted device provisions in section 520(e) of the Act. After almost 23 years FDA has yet to effect rulemaking to implement the restricted device provisions under section 520(e) for the vast majority of marketed devices. The draft guidance inappropriately cites section 515(d)(1)(B)(ii) of the Act as granting FDA the authority to restrict the use of the reclassified ESWLs. As indicated in the proposed rule, the correct citation is section 520(e) of the Act. The draft 510(k) guidance and the Appendix (Labeling Restrictions) to 21 CFR 876.5990 in the proposed rule should be revised to both include this suggested revision of the restricted device legend and to indicate that it must appear on the device label and in all labeling for the device. Mention of the restricted use of this device appears in the preamble of the proposed rule but not in the text of proposed 21 CFR 876.5990.

The Appendix to 21 CFR 876.5990 in the proposed rule and the draft guidance provide for standardized information regarding the expected frequency of potential adverse events. The final rule and final ESWL 510(k) guidance need to clarify that a PMA holder, at its option, can continue to include in its labeling the adverse event data from the clinical studies supporting its PMA approval in lieu of this standardized information. FDA approval of a PMA is based upon a determination that the PMA includes sufficient valid scientific evidence to provide reasonable assurance of the device's safety and effectiveness for its intended use. The safety and effectiveness information in the PMA approved labeling was subjected to a stringent FDA statistical review. Use of the standardized adverse event information is appropriate, and should be required, when the clinical study data in the applicant's 510(k) does not meet the PMA approval criteria or does not build upon the device-specific safety and effectiveness information contained in an approved PMA held by the same applicant.

Physician Training Program

The restricted device legend in the draft 510(k) guidance and the preamble of the proposed rule clearly indicates that the required physician training must extend beyond providing each physician, who intends to use the firm's ESWL, with training materials. FDA apparently intends that there be some form of documented hands-on training or appropriately supervised use of the device. Lack of consistency in the physician training programs cleared via 510(k)s could create significant product liability and litigation issues for manufacturers and physicians. Because of the 15-year experience with the use of ESWLs in the United States, FDA should not require that in all cases the hands-on training or supervision be provided by a trained representative of the manufacturer. Training by a physician already trained or experienced in the use of the manufacturer's ESWL should suffice. FDA should provide guidance as to how this required training is to be documented and how the documentation is to be maintained.

FDA Regulation of Replacement ESWL Shock Plugs and Other Replacement Parts

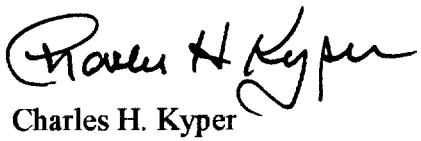
On September 6, 1990, FDA approved a PMA (P870011) for an ESWL shock plug as a replacement component for a specific model of a competitor's ESWL. FDA has required this PMA holder to obtain PMA supplement approval each time it develops a replacement shock plug for an additional ESWL model. When marketed under a 510(k) clearance, these replacement shock plugs will be held to a lesser standard in terms of when additional FDA clearance is required for modifications needed for its use in additional ESWLs. Once the final reclassification rule becomes effective, other firms may see an opportunity to manufacture and market replacement shock plugs and other replacement parts for use in another firm's ESWL because of the less stringent 510(k) provisions. Unless the marketing of these replacement parts is adequately regulated by FDA, this could adversely affect the public health and result in needless product liability and litigation problems for ESWL manufacturers.

The proposed rule does not indicate that the safety and effectiveness information in the approved PMA referenced above was used to reclassify ESWLs. It also does not indicate

that the proposed reclassification and draft 510(k) guidance apply to the manufacture and marketing of replacement shock plugs and other replacement parts for use in another firm's ESWL. FDA needs to clarify this matter in the final reclassification regulation and 510(k) guidance. If FDA determines that the reclassification applies to replacement ESWL parts for use in another firm's ESWL, appropriate 510(k) guidance applicable to these replacement parts should be provided.

We hope that the enclosed comments are helpful. Please do not hesitate to contact me if additional information or clarification is needed.

Sincerely,



Charles H. Kyper
President

Enclosure

Kyper & Associates

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March 17, 1999

Dockets Management Branch (HFA-305)
Food and drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 98D-1165
Draft Guidance for the Content of Premarket Notifications [510(k)s] for Electrocorporeal Shock Wave Lithotripters Indicated for the Fragmentation of Kidney and Ureteral Calculi

Dear Sir/Madam:

On behalf of a holder of an approved premarket approval application (PMA) for an electrocorporeal shock wave lithotripter (ESWL), I am submitting the enclosed comments on the above referenced draft guidance. My client is supportive of the FDA proposed rule to reclassify ESWL devices into Class II. On their behalf I will be submitting comments on the proposed rule under separate cover. Our enclosed comments on the draft guidance will address the provisions in the same order as they appear in the document. We conclude our comments by addressing an issue not specifically covered in the draft guidance, i.e., the regulation of replacement ESWL shock plugs.

Page 3: Predicate Device

Section 216 of the FDA Modernization Act of 1997 (FDAMA) amended section 520(h)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) to make available safety and effectiveness information in an approved PMA for FDA use, among other things, in approving or reclassifying another device 6 years after FDA approval of the PMA. The publicly available summaries of safety and effectiveness information required by section 520(h)(1)(A) of the Act are thereby available to FDA as the evidentiary basis for FDA approval or reclassification of another device.

In light of this FDAMA provision, FDA should revise the draft guidance to require 510(k) applicants to demonstrate that the cited predicate device is legally marketed under either a FDA cleared 510(k) submission or an original PMA/PMA supplement approved at least 6 years prior to the submission of the applicant's 510(k).

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Citation of a modified version marketed under an approved PMA supplement, however, may not be possible as a publicly available summary of the safety and effectiveness data does not presently exist for ESWL models or modifications marketed via PMA supplement approval. Until at least one firm has obtained 510(k) clearance for such a modified device, a competitor's predicate device cited by a 510(k) applicant should be limited to that in the competitor's original PMA. The 510(k) applicant should then be required to address the differences in technological characteristics as prescribed in an applicable FDA law, regulation and guidance to demonstrate that no new issues of safety or effectiveness exist and its device is as safe and effective as the cited predicate device. FDA needs to address this PMA supplement issue if it proceeds to finalize this reclassification of ESWLs..

As an aid to 510(k) applicants in identifying appropriate predicate devices, FDA should include in the guidance a revision of the chronological listing of PMA/PMA supplement approvals currently available through the CDRH web site. Revisions of most listings are needed to identify the device model number(s) or modification(s) covered by the PMA/PMA supplement approval.

Page 4: Intended Use

The suggested indication for use in the draft guidance is inconsistent with that in PMA/PMA supplement approvals for ESWLs to date. In the latter case FDA has in certain cases placed limitations on the size range of the urinary stones to be fragmented and the region of the ureter to be treated. This usually occurs when there is an insufficient number of appropriate patients enrolled in the clinical study to support a broader indication for use. No such limitations appear in the intended use suggested in the draft guidance. It appears that the 510(k) applicant can label its ESWL for use in fragmenting all size stones and those in the upper, middle, lower or entire ureter without FDA requiring sufficient valid scientific evidence to support this broad intended use. If FDA proceeds with the reclassification, the final guidance and final classification rule need to clarify this issue and, if appropriate, indicate what holders of approved PMAs must do to remove any existing limitations in the indications for use of their ESWL.

Page 8: Clinical Performance Testing

The suggested confirmatory clinical study for demonstrating substantial equivalence would permit as few as 20 patients to be enrolled at two investigational sites with only a follow-up at 1-week post-procedure. The guidance is unclear whether there should be at least 20 patients at each of two sites or a total of 20 patients between two sites. Either way, a clinical study of such low magnitude does not lend itself to any meaningful statistical evaluation. On a random selection basis, it would not be expected to enroll patients representative of the patient population in the indication for use suggested in this draft guidance and discussed in the preceding paragraph. If the final guidance continues to provide for confirmatory clinical studies of this low magnitude, it should justify the adequacy of such studies in demonstrating substantial equivalence. This is especially necessary as neither the draft guidance nor the proposed reclassification rule cite postmarket surveillance as one of the special controls deemed necessary to demonstrate in a 510(k) submission that a new or modified ESWL is as safe and effective as the cited predicate device(s).

For a new or significantly modified ESWL with an operating principle and shock wave characteristics similar to the cited predicate device(s), a confirmatory clinical study for demonstrating substantial equivalence should involve at least 3 investigational sites, a minimum of 30 patients per site, and the assessment of treatment success and adverse effects immediately post-procedure and at 2-weeks and 1-month thereafter. This study lends itself to a meaningful statistical evaluation and should allow for a study population representative of the intended use. It should also permit the 510(k) applicant and FDA to determine whether the success rate is consistent with marketed ESWLs and whether its adverse event experience is consistent with the standardized adverse event information to be required in the labeling.

We support the provision on page 9 of the draft guidance that the addition of device-specific claims regarding the clinical performance of the applicant's ESWL must be demonstrated by sufficient clinical data to statistically support the claim. The draft guidance should be revised to clearly indicate that such a claim requires FDA clearance of a 510(k) before it can be included in the firm's labeling, advertisements, and other promotional materials for its device. We are concerned, however, that FDA apparently lacks the authority to revoke 510(k) clearances and may grant 510(k) clearances for comparative performance claims based upon erroneous or unsupportable information. The confirmatory clinical studies suggested in the draft guidance will not provide a study population comparable to those in approved PMAs and cannot support claims of superior safety and effectiveness. We suggest that the guidance clearly indicate that FDA will not accept 510(k) submissions for comparative performance claims as such claims are inappropriate for 510(k) review and, in all likelihood, unsupportable for substantially equivalent devices. The guidance should identify the types of clinical performance claims that are appropriate for 510(k) review and clearance.

Page 9: Labeling

The guidance inappropriately cites section 515(d)(1)(B)(ii) of the Act as the authority for restricting the device to physicians trained and/or experienced in the use of the device as outlined in the required training program. This is the statutory authority that applies to PMA approval orders only and is cited in the PMA approval orders for ESWLs and most other PMA approved devices. In addition to restricting the use of the PMA approved device, it implements the FDA authority to regulate its advertising. FDA is required to go through a rulemaking process in order to designate other devices as restricted devices. The proposed reclassification rule published in the February 8, 1999 *Federal Register* appropriately cites section 520(e) of the Act as the authority to restrict the use of the reclassified ESWLs.

Because ESWLs are presently, and will continue to be, restricted devices and not simply prescription devices under 21 CFR 801.109, the restricted device legend should be revised to read:

> "CAUTION: Federal law restricts this device to sale, distribution, and use only upon the lawful order of a physician trained and/or experienced in the use of this device as outlined in the required training program."

The legend on pages 9 and 19 (Appendix 2: SWL Labeling Template) in the draft guidance is consistent with 21 CFR 801.109 but only restricts the sale, and not the distribution and use, of the device. This suggested revision more appropriately conforms to the provisions in section 520(e) of the Act for restricted devices.

Pages 12 and 13 of the draft guidance provide for standardized information regarding the expected frequency of potential adverse events. The guidance needs to clarify whether a firm can continue to include in its labeling the adverse event data from the clinical studies supporting its PMA approval in lieu of the standardized information. We suggest that the PMA holder be given an option in this matter. FDA approval of a PMA is based upon a determination that the PMA includes sufficient valid scientific evidence to provide reasonable assurance of the device's safety and effectiveness for its intended use. Use of the standardized adverse event information is appropriate, and should be required, when the clinical study data in the applicant's 510(k) does not meet the PMA approval criteria for providing reasonable assurance of safety and effectiveness or does not build upon the safety and effectiveness information contained in an approved PMA held by the same applicant.

Page 14: Training Program

The restricted device legend required in the device labeling clearly indicates that the required physician training must extend beyond simply providing each physician, who intends to use the firm's ESWL, with training materials such as a User's Manual or a videotape demonstrating the use of the device. FDA apparently intends that there be some form of documented hands-on training or appropriately supervised use of the device.

Lack of consistency in the physician training programs cleared via 510(k)s could create significant product liability and litigation issues for manufacturers and physicians. The final guidance should include information needed to provide this consistency. Because of the 15-year experience with the use of ESWLs in the United States, FDA should not require in all cases that the hands-on training or supervision be provided by a trained representative of the manufacturer. Training by a physician already trained and experienced in the use of the manufacturer's ESWL should suffice. FDA should offer suggestions as to how this training is to be documented and how the documentation is to be maintained.

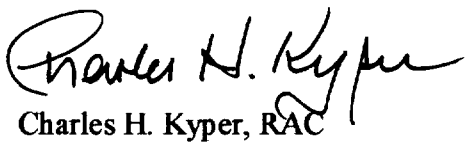
Regulation of Replacement ESWL Shock Plugs

On September 6, 1990, FDA approved a PMA (P870011) for an ESWL shock plug as a replacement component for a specific model of a competitor's ESWL. PMA supplement approval with supporting clinical studies beyond those suggested in the draft guidance is required each time the manufacturer develops a replacement shock plug for an additional ESWL model. Under section 216 of FDAMA the safety and effectiveness information in this PMA is now available for FDA use to allow firms to market replacement shock plugs for any and all marketed ESWLs via the 510(k) process.

The proposed reclassification rule and draft ESWL guidance, however, do not indicate whether the proposed reclassification applies to replacement ESWL shock plugs when manufactured and distributed by a firm other than the manufacturer of the ESWL. FDA needs to clarify this matter in both the final reclassification rule and the associated guidance. The guidance may need to have a specific section addressing the 510(k) content requirements for firms that manufacture and market replacement shock plugs for ESWLs other than their own. The draft ESWL guidance directs the reader to another FDA document for guidance when additional 510(k) clearance is needed for a modification of a marketed device. Because this latter guidance is not device-specific and lends itself to varying interpretations, we suggest that the final ESWL guidance require these firms to obtain 510(k) clearance when they propose to market a replacement shock plug for an additional model of a another firm's marketed ESWL. Each 510(k) clearance should be supported by a clinical study of sufficient magnitude to demonstrate that the clinical performance of the replacement shock plug is comparable to that of the shock plug supplied by the ESWL manufacturer.

We hope that the enclosed comments are helpful. Please do not hesitate to contact me if additional information or clarification is needed.

Sinncerely,



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President

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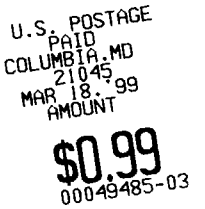

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